Michael Garvin, Pharm.D.
Director
Scientific and Regulatory Affairs

PhRMA

January 14, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Request for Comments on a Draft Guidance for Industry on Pharmacokinetics in Pregnancy-Study Design, Data Analysis, and Impact on Dosing and Labeling [Docket No. 2004D-0459, 69 *Federal Register*, 63402-63403, November 1, 2004]

Dear Madam/Sir:

The attached comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA is a voluntary, non-profit trade association representing the firms that discover, develop and produce prescription drugs and biologic products. The large majority of new prescription medicines approved for marketing in the United States are produced by PhRMA member firms.

A PhRMA Joint Committee team has carefully reviewed the draft guidance and appreciates the opportunity to provide comments on the "Draft Guidance for Industry on Pharmacokinetics in Pregnancy-Study Design, Data Analysis, and Impact on Dosing and Labeling."

General Comments:

There is a general sense that pharmacokinetic (PK) studies in pregnancy would be difficult to conduct with design requirements and PK/PD evaluations typically used in Phase I studies using healthy volunteers. The requirements of typical patient population including race and ethnicity, extensive PK sampling, sample size and the use of 90 % confidence interval analysis would appear to be restrictive. Furthermore, an inherent assumption in using PK and/or PK/PD in making dosage adjustment is that dose response relationship is unaffected by pregnancy and that good correlation between PK and relevant biomarkers of response exist.

Guidelines for participation of pregnant women in pharmacokinetic studies: The risk/benefit for participation of pregnant women in pharmacokinetic studies appear to fit into at least two general categories – studies that will be conducted in women with pre-

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existing or concurrent conditions and those that will include participants on a voluntary basis (i.e., drug evaluated is not required during pregnancy). These categories may differ with respect to risk/benefit to the woman and/or to the fetus. For example, risk to the pregnant woman would be greater if a pre-existing/concurrent condition went untreated and participation in a study would not pose a greater risk to the fetus since drug treatment is required regardless of participation. For women who do not require treatment during pregnancy, the risk/benefit for participation will be more difficult to assess. As suggested in the draft Guidance, it will be important to consider safety/efficacy data in women from Phase III studies (i.e., for assessment of risk to the pregnant woman). However, it is suggested that minimal risk to the fetus would be based on pre-clinical data although the predictability of such data is not currently known. Therefore, establishing risk to the fetus in these cases will be difficult.

Specific Comments

Line 33 Section 1. Introduction

Comment: Although this guidance states that it is not intended to assess the efficacy of a drug in pregnancy, it does assume no change in the exposure-response relationship when it recommends labeling changes based on PK. Recommendations for label changes based on PK data from pregnant women assume that the exposure-response relationship is not affected by the pregnancy condition.

Line 152 Section III. Deciding whether to conduct a pharmacokinetic study in pregnant women

Comment: We request greater clarity around how post marketing exposure and safety data will be assessed to determine the need for PK studies

Line 162 Section III. Deciding whether to conduct a pharmacokinetic study in pregnant women

Comment: In these rare cases, it should be specified that only women with the disease in question and who require treatment will be used in these studies as it would not be recommended to expose other pregnant women to, for example, narrow therapeutic range drugs.

Line 198 . Study Design A. Longitudinal Design
Although the longitudinal design, from a theoretical point of view, would be the preferred design, FDA should consider use of a parallel design to assess clinically important (major) changes, which would be more consistent with the use of the population PK approach.

Line 179 Section IV. Study Design

Comment: Practical considerations for obtaining baseline pharmacokinetics: There are two possible timeframes suggested in which baseline pharmacokinetic values should be obtained – prepregnancy or postpartum. Both of these may be limited for practical reasons. For prepregnancy determinations, the investigator would have to obtain informed consent prior to the subject becoming pregnant, making it difficult to recruit subjects who are trying to become pregnant and also are willing to participate in a Phase I study. Identifying such subjects would require the involvement of a network of referring obstetricians or academic centers committed to such research (typical Phase I CROs would likely not have such women in their databases and/or be equipped to follow subjects throughout the 9-month term). As an alternative, the draft guidance suggests that baseline determinations optimally should be taken in the postpartum period and while not lactating. Since it is known that cardiovascular and renal changes do not return to baseline until 3 months postpartum, and since current recommendations from the American Academy of Pediatrics are that breastfeeding should "continue for at least 12 months," baseline determinations will be difficult to obtain from a practical perspective. In addition, scientifically, baseline determinations may be obtained at different time points postpartum.

Line 179 Section IV. Study Design

Comment: The document mentions the usual PK parameters such as Area Under the Curve (AUC), for analysis. To collect full profile every trimester from pregnant women appears to be excessive. Since these are expected to be at steady-state, we believe Ctrough and Cmax may be sufficient, instead of a full profile.

Line 181 Section IV. Study Design

Comment: The guidance assumes that if PK and/or PD are altered enough then there would be a requirement for dosage adjustment. This assumes an unchanged exposure-response relationship. Also, what if there is poor correlation between PK and PD such that PK changes are not important for the efficacy of the drug. In case of drug products for which PK changes are known to be poorly correlated with pharmacodynamic responses and clinical endpoints, PK changes in pregnancy would be of little value.

Lines 190-191 Section IV. Study Design

Comment: Lines 190-191 state that postpartum PK/PD assessments would be best done when a woman is neither pregnant nor lactating. Does the guidance suggest that sponsors recruit women who do not plan to breast feed their babies since lines 287-289

suggest assessment schedule postpartum? The suggested schedule will not be possible if a woman is lactating.

Line 193 Section IV. Study Design

Comment: What is the rationale for determining the PK differences in drugs dosed to effect? For certain indications such as hypertension and asthma, these agents are dosed based on accepted clinical endpoints and not necessarily to achieve the certain blood concentration.

Line 198 Section IV. Study Design A. Longitudinal Design

Comment: Investigator-defined windows for PK/PD assessments during a given trimester: In Section IV. A. Longitudinal Studies, the guidance suggests that because many changes occur within a given trimester, assessments should be obtained within a narrow window of time e.g., a 4-week window per trimester. However, results (PK and/or PD) may differ depending upon when the window occurs in a given trimester (physiologically, one is different at the beginning of the 2nd trimester than at the end). Moreover, if different investigators obtain assessments in different windows of time, it will be difficult to compare across studies. One possibility would be to use a population PK approach since week of pregnancy can be used as a covariate in the analysis. Otherwise, perhaps a standard recommendation could be given that the last 2 to 3 weeks of a given trimester is when assessments should be obtained.

Line 212-216 Section IV. Study Design

Comment: It is unclear why one should use a window for visits since this would appear to provide less information than collection data at various time during each trimester and analyzing the data as a continuous variables versus categorical.

Lines 241-243 Section IV. Study Design B. Population PK Design

Comment: Practical considerations for studies with a population PK design: Although the population PK approach may be optimal for conducting studies in pregnant women in several respects, it is not clear how data will be obtained. Many Phase III-type sites are not equipped to obtain PK samples and provide the appropriate handling and storage and there is no 'network' of experienced obstetricians for collaboration in conducting such studies. Thus, there is a need for Phase-III sites with Phase I capabilities.

Lines 241-243 Section IV. Study Design B. Population PK Design

Comment: Lines 241-243 recommend including matched healthy non-pregnant female volunteers in population PK studies. This suggestion seems impractical since there are very few healthy volunteers in a regular population PK study that collects PK information in patient population from phase II, III, and IV studies. If a pregnancy PK is desired for the drug development program, it seems more cost-effective to recruit more healthy non-pregnant female volunteers in earlier phase I studies to allow for a retrospective matching-control analysis. A stronger consideration would be to leave out Section IV. B. completely as an alternative. It would likely to complicate entire population PK study by adding in another pregnancy covariate.

Line 243 Section IV. Study Design : "To ensure the ability to determine in inter-occasion variability and prevent a parallel group trial design, a cohort of study subjects would have data collected from all trimesters and the postpartum period."

Comment: This requirement represents an added burden on the study design and conduct and runs counter to the population PK design approach. We suggest eliminating this requirement.

Line 259 Section V. Other Design Considerations: Study Participants

Comment: Given the likely small size of these studies, trying to make the patient population "typical" may not be possible. These factors should have been dealt with in the label already.

Line 292 Section V. Other Design Considerations: postpartum assessments

Comment: For drugs that posses linear kinetics among normal volunteers, can we assume linear kinetics among pregnant women also? (line 292-295).

Line 292 Section V. Other Design Considerations: postpartum assessments

Comment: <u>Comparison between single-dose postpartum PK and multiple-dose pregnancy PK</u>: In Section V. B., the guidance states that if PK is linear, single-dose postpartum data can be compared to multiple-dose data during pregnancy. Although PK may be linear postpartum, it is possible that PK is not linear during pregnancy and therefore these comparisons may not be valid. In addition, it is noted that PK may change in weeks to months postpartum and therefore different drugs may require a different amount of time to when PK is linear again. This would have to be studied before the appropriate timing for postpartum baseline assessments can be determined.

Line 303 Section V. Other Design Considerations: C. Sample Size

Comment: Practical issues with obtaining a sufficient sample size: A sufficient number of subjects may be difficult to obtain given inherent PK variability of a given drug plus variability during pregnancy. It is also possible that the drop-out rate may be high in such studies, especially postpartum (i.e., subjects would have to return for study assessments only which may not be part of the routing follow-up schedule). Given these concerns, a very wide net will need to be cast to obtain sufficient number of participants. Moreover, until the variability in PK during pregnancy is known, inclusion of such data in sample size determinations may not be possible.

Line 357 Section V. Other Design Considerations: F. Studies with No Intended Therapeutic Benefit

Comment: While this guidance focuses on PK/PD in pregnant women, there ought to be some statement regarding evaluating the outcome of the pregnancy, i.e., if the pregnancy results in a normal birth. This seems to be especially relevant in section V.F when there is no intended therapeutic benefit for the pregnant women in the study.

Line 416 Section VI. Data Analysis: B. Development of Dosing recommendations

Comment: Dosing recommendations can only be offered on the basis of PK if we assume there is no change in the exposure response relationship.

Line 466 Section VII. Labeling: A. Clinical Pharmacology: 1. Pharmacokinetic Subsection: Effects of changes in urinary pH or other special situations (e.g., tubular secretion inhibited by probencid)

Comment: Please clarify why this section is included in the guidance?

Line 497 Section VII. Labeling: A. Clinical Pharmacology: 2. Special Populations:

Comment: This implies that the efficacy was evaluated, which is beyond the scope of this guidance

Line 414 Section VII. Labeling: B. Development of dosing recommendations:

Comment: Given the typical solid dosage form strengths, dosage adjustment might be difficult from a practical sense. Also the 90% CI are too restrictive for this type of study.

Thank you for considering these comments as you finalize the guidance. Please contact me if you have any questions.

Sincerely,

Michael Garvin

Michael Garvin, Pharm.D.